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Prediction of High-Risk Plaque Development and Plaque Progression With the Carotid Atherosclerosis Score

Dongxiang Xu, PHD,* Daniel S. Hippe, MS,* Hunter R. Underhill, MD, PHD,† Minako Oikawa-Wakayama, MD,‡ Li Dong, MD,§ Kiyofumi Yamada, MD, PHD,* Chun Yuan, PHD,* Thomas S. Hatsukami, MD‖

Seattle, Washington; Sendai, Japan; and Beijing, China

OBJECTIVES The goal of this prospective study was to evaluate the carotid atherosclerosis score (CAS) for predicting the development of high-risk plaque features and plaque burden progression.

BACKGROUND Previous studies have shown that carotid intraplaque hemorrhage (IPH) and a disrupted luminal surface (DLS), as identified by using magnetic resonance imaging, are associated with greater risk for cerebrovascular events. On the basis of data from a large cross-sectional study, a scoring system was developed to determine which plaque features are associated with the presence of IPH and DLS. However, the predictive value of CAS has not been previously tested in a prospective, longitudinal study.

METHODS A total of 120 asymptomatic subjects with 50% to 79% carotid stenosis underwent carotid magnetic resonance imaging scans at baseline and 3 years thereafter. Presence of IPH and DLS, wall volume, maximum wall thickness, and maximum percent lipid-rich necrotic core area were measured at both time-points. Baseline CAS values were calculated on the basis of previously published criteria.

RESULTS Of the 73 subjects without IPH or DLS at baseline, 9 (12%) developed 1 or both of these features during follow-up. There was a significant increasing trend between CAS and the development of new DLS ($p < 0.001$) and with plaque burden progression ($p = 0.03$) but not with the development of new IPH ($p = 0.3$). Percent carotid stenosis was not significantly associated with new DLS ($p = 0.2$), new IPH ($p = 0.1$), or plaque progression ($p = 0.6$).

CONCLUSIONS CAS was found to have a significant increasing relationship with incident DLS and plaque progression in this prospective study. CAS can potentially provide improved risk stratification beyond luminal stenosis. (J Am Coll Cardiol Img 2014;7:366–73) © 2014 by the American College of Cardiology Foundation

From the *Department of Radiology, University of Washington, Seattle, Washington; †Departments of Neurological Surgery and Medicine, University of Washington, Seattle, Washington; ‡Department of Radiology, Tohoku University, Sendai, Japan; §Department of Radiology, Anzhen Hospital, Beijing, China; and the ‖Department of Surgery, University of Washington, Seattle, Washington. The study was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health under award numbers R01HL061851, R01HL073401, R01HL67406, and T32HL7838. The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health. Dr. Xu is a consultant of VPDiagnostics. Mr. Hippe has received research grants from Philips Healthcare and GE Healthcare. Dr. Yuan has received research grant support from the National Institutes of Health, Philips Healthcare, and VPDiagnostics; and has been a

Stroke is one of the leading causes of mortality and morbidity worldwide, and carotid atherosclerotic disease is a primary etiologic factor (1,2). Currently, the risk of stroke associated with carotid atherosclerosis is stratified according to the severity of luminal stenosis (3). Several large prospective clinical trials (4–6) have supported intervention with carotid endarterectomy (CEA) or stenting for symptomatic patients with >70% stenosis to reduce stroke risk. However, for symptomatic patients with <70% stenosis and for asymptomatic patients, stenosis alone may not be a reliable measure of stroke risk. A growing body of evidence suggests that plaque composition, as detected using magnetic resonance imaging (MRI) rather than luminal narrowing, is the critical factor governing risk of ischemic cerebrovascular events originating from the carotid artery (7–12). Specifically, the presence of a disrupted luminal surface (DLS) (e.g., fibrous cap rupture [FCR], ulceration) and/or intraplaque hemorrhage (IPH) is indicative of a high-risk lesion for ischemic events (13–16).

Although results from studies to better characterize carotid atherosclerosis using MRI hold great promise, progress toward its translation into clinical practice has been hindered by the complex nature of analysis of the multicontrast-weighted images. A simple-to-use method to classify plaque that has predictive value for carotid lesion progression and future ischemic events is essential to move the field forward.

In a cross-sectional study of 435 subjects from 4 imaging sites in the United States and China, Underhill et al. (17) proposed a rapid risk stratification strategy, known as the carotid atherosclerosis score (CAS), based on maximum wall thickness (WT) and the maximum lipid-rich necrotic core percentage (%LRNC). Statistical analysis found that CAS was an accurate predictor for the presence of IPH and FCR in the test subgroup of this single time-point study. Furthermore, when compared with stenosis measured using magnetic resonance angiography, CAS was a stronger classifier of high-risk features.

Although CAS was successfully designed and tested in a cross-sectional study (17), it is unclear if it can predict the development of high-risk plaque features and plaque burden progression in a prospective, longitudinal study. The goals of the present study were to: 1) investigate the associations between the CAS, incident IPH, or DLS and plaque burden progression during follow-up; and 2) to compare CAS and stenosis in risk prediction among asymptomatic individuals with 50% to 79% carotid stenosis.

METHODS

Study subjects. Subjects with 50% to 79% carotid stenosis on at least 1 side consented to be recruited into this study at the University of Washington Medical Center and the Veterans Affairs Puget Sound Health Care Systems. Carotid stenosis was determined with duplex sonography using the Strandness criteria (18). The side with greater stenosis was defined as the index artery. All subjects were asymptomatic with regard to their carotid disease for the 6 months before recruitment. One hundred twenty subjects underwent a baseline carotid MRI and follow-up scan 3 years thereafter.

Subjects with any of the following conditions were excluded: 1) CEA before or during the study on the index carotid artery; 2) previous radiation therapy to the neck; and 3) contraindication to MRI.

MRI. All subjects underwent MRIs at baseline and at the 3-year follow-up on a 1.5-T scanner (Signa Version 5.8, GE Healthcare, Milwaukee, Wisconsin) with a bilateral, 4-element, phased array surface coil (Pathway MRI, Seattle, Washington). A multicontrast protocol for carotid MRI (19) was used to acquire axial images with the parameters listed in Table 1.

Image analysis. The index arteries of all subjects were interpreted via consensus opinion by 2 experienced reviewers who received certified training at the Vascular Imaging Laboratory, University of Washington, Seattle, Washington. Both reviewers were blinded to the time-point and clinical information during image analysis. For each scan, multicontrast magnetic resonance images were aligned using the carotid bifurcation as a landmark. At each registered axial slice, images were graded for image quality on a 4-point scale in which 1 = poor and 4 = excellent. Slices with image quality ≥2 at both time-points were interpreted using

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CAS = carotid atherosclerosis score
CEA = carotid endarterectomy
CI = confidence interval
DLS = disrupted luminal surface
FCR = fibrous cap rupture
IPH = intraplaque hemorrhage
LRNC = lipid-rich necrotic core
MRI = magnetic resonance imaging
NWI = normalized wall index
WT = wall thickness

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Table 1. Multicontrast MRI Imaging Parameters

	T1w	T2w	PDw	TOF
Readout pulse	2D FSE	2D FSE	2D FSE	3D spoiled GRE
TR, ms	800	2,770	2,770	23
TE, ms	10	40	20	3.8
FOV	16 × 16	16 × 16	16 × 16	16 × 16
Matrix	256 × 256	256 × 256	256 × 256	256 × 256
Slice thickness, mm	2.0	2.0	2.0	2.0
NEX	2	2	2	2
No. of slices	12	12	12	24
Blood suppression	DIR	Multislice DIR	Multislice DIR	Venous in-flow saturation
Slice gap, mm	0	0	0	−1.0
Flip angle	90	90	90	35
Scan time, min	8	4	4	4

DIR = double inversion recovery; FOV = field of view; FSE = fast spin echo; GRE = gradient recalled echo; MRI = magnetic resonance imaging; NEX = number of excitations; PDw = proton density-weighted; T1w = T1-weighted; T2w = T2-weighted; TE = echo time; TOF = time-of-flight; TR = repetition time.

vascular image analysis software (CASCADE, Vascular Imaging Laboratory, University of Washington) (20). After drawing the lumen and outer wall boundaries on each slice, plaque burden measurements were derived, including wall area and volume, maximum WT, and mean normalized wall index (NWI). NWI was computed per slice as: wall area/(lumen area + wall area). Based on validated analysis criteria (21–23), IPH, LRNC, FCR, and ulceration were identified. The %LRNC was also recorded per slice, where %LRNC = 100% × (LRNC area/wall area). Using the carotid bifurcation as a landmark, scans from the 2 time-points were matched, and artery-based measurements were computed from the common coverage for each subject. The inter-reader and interscan reproducibility of these measurements has been reported in previous studies (24,25).

Table 2. Summary of Patient Demographic Characteristics and Baseline Plaque Burden at Baseline (N = 73)

	Value	Range
Age, yrs	70.3 ± 9.6	45–89
Body mass index, kg/m^2*	27.7 ± 5.4	18.9–54.3
Systolic blood pressure, mm Hg*	144 ± 21	99–194
Male	62 (85)	–
Smoking status*		
Never smoked	10 (14)	–
Quit	37 (51)	–
Active	25 (35)	–
Diabetes mellitus*	19 (26)	–
History of coronary artery disease*	31 (46)	–
History of hypertension	62 (85)	–
History of hypercholesterolemia	61 (84)	–
Statin therapy	51 (70)	–
Carotid stenosis, %†	29 ± 21	0–77
Wall volume, mm^3	660 ± 228	249–1,327
Mean normalized wall index	0.52 ± 8.00	0.36–0.74
Maximum wall thickness	3.4 ± 1.2	1.3–7.7

Values are mean ± SD or n (%). *Excluding subjects missing measurement: 7 for body mass index, 1 for smoking status, and 5 for history of coronary artery disease. †Measured from 3-dimensional time-of-flight magnetic resonance angiography using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.

The severity of carotid stenosis was quantified based on magnetic resonance angiography images rendered from time-of-flight data by a trained reviewer who was blinded to clinical information and cross-sectional carotid magnetic resonance images. Luminal stenosis was measured on the index side of the carotid artery using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria: 1 − (luminal diameter at the location with maximal narrowing/luminal diameter of normal distal internal carotid artery) × 100% (4). All measurements were acquired on maximum intensity projection images with CASCADE.

CAS was computed from the maximum WT and maximum %LRNC measurements, in which maximum %LRNC represented the cross-sectional slice with the largest %LRNC value for the index carotid artery. CAS was determined as follows: CAS = 1 if maximum WT ≤2 mm; otherwise, if maximum WT >2 mm, CAS was set according to maximum %LRNC; CAS = 2 if maximum %LRNC was <20%, CAS = 3 if maximum %LRNC was between 20% and 40%, and CAS = 4 if maximum %LRNC was >40%.

Statistical analysis. Plaque variables were aggregated over the slices within each artery, in which only slices present in scans at both time-points were included. Arteries with <10 mm of common coverage were excluded. Patient demographic characteristics were summarized using mean ± SD and range for continuous measurements and count (percentages) for categorical variables. The chi-square test for trend was used to test for an increasing association between CAS and new high-risk features.

Plaque progression was defined as the annualized wall volume change between time-points. Subjects who developed ulcerations over the follow-up period were excluded from the analysis of plaque progression because morphology measurements (lumen and wall volumes) were confounded by the presence of ulceration. Plaque progression was summarized

Table 3. Incidence of New DLS or IPH According to Baseline CAS (73 Subjects Without DLS or IPH at Baseline)

		n (%)†		
Baseline CAS	**n (%)***	**DLS**	**IPH**	**DLS or IPH**
1	8 (11)	0 (0)	0 (0)	0 (0)
2	51 (70)	0 (0)	2 (4)	2 (4)
3	10 (14)	4 (40)	2 (20)	4 (40)
4	4 (5)	3 (75)	0 (0)	3 (75)
All	73 (100)	7 (10)	4 (5)	9 (12)
p for trend test		<0.001	0.264	<0.001

*Percentage of total (N = 73). †Percentage of subjects counted in each row (see second column).
DLS = disrupted luminal surface; IPH = intraplaque hemorrhage.

as mean ± SD for the whole group and for each subgroup defined according to the baseline level of CAS. The progression rate was compared with 0 using the 1-sample Student *t* test. Linear regression was used to test for an increasing trend between the baseline CAS and plaque progression.

Receiver-operating characteristic curves and the area under the curve (AUC) statistic were used to summarize the strength of the association between new DLS or IPH and CAS, carotid stenosis, and plaque burden (wall volume, mean NWI, and maximum WT). Pearson correlation coefficient was used similarly with the same predictors and plaque progression as the outcome.

All statistical analyses were performed using R version 2.11.0 (R Foundation for Statistical Computing, Vienna, Austria). Throughout, 2-tailed tests were used, with $p < 0.05$ denoting statistical significance.

RESULTS

Of the 120 subjects recruited, 20 were excluded: 12 with poor image quality at either time-point, 7 with insufficient coverage, and 1 subject who underwent CEA during the study period. To evaluate the association between CAS and incident IPH and DLS, 73 of 100 subjects without these features at baseline were analyzed. The mean time interval between baseline and follow-up scans was 3.0 ± 0.2 years. Demographic information and baseline plaque measurements of these 73 subjects are shown in Table 2.

Incidence of new high-risk features. The incidence of new DLS or IPH among the 73 subjects without these features at baseline is summarized in Table 3. At follow-up, 7 subjects developed DLS (including 2 ulcerations) and 4 developed IPH (2 of which

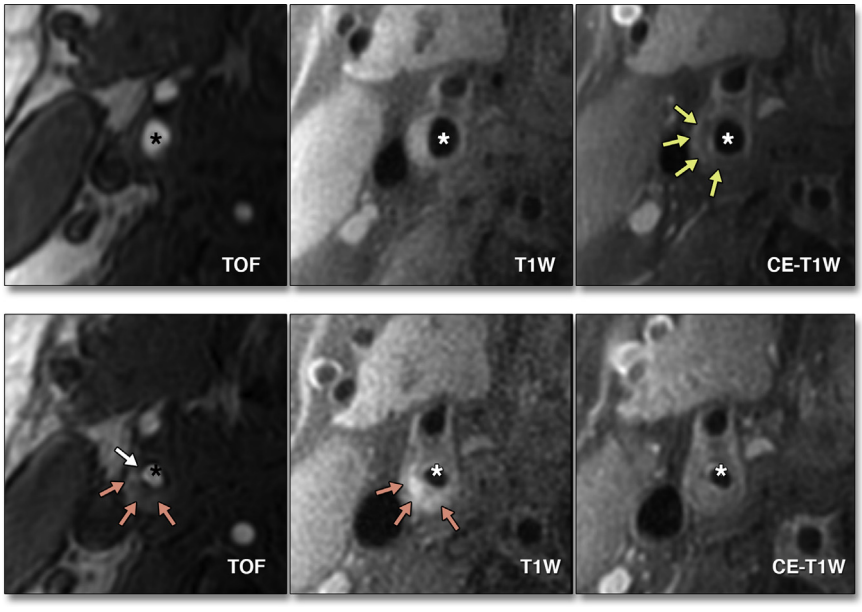

Figure 1. Baseline MRI Demonstrating a CAS 4 Internal Carotid Plaque With a Large LRNC

Baseline magnetic resonance imaging (MRI) **(top row)** with a large lipid-rich necrotic core (LRNC) **(yellow arrows)**. The 3-year follow-up MRI **(bottom row)** of the matched cross-section demonstrates fibrous cap rupture **(white arrow)** with intraplaque hemorrhage **(pink arrows)**. Also note the large increase in internal carotid wall area and decrease in lumen area. *Lumen of the internal carotid artery. CAS = carotid atherosclerosis score; CE-T1W = post-contrast enhanced T1-weighted image; T1W = pre-contrast T1-weighted image; TOF = time-of-flight.

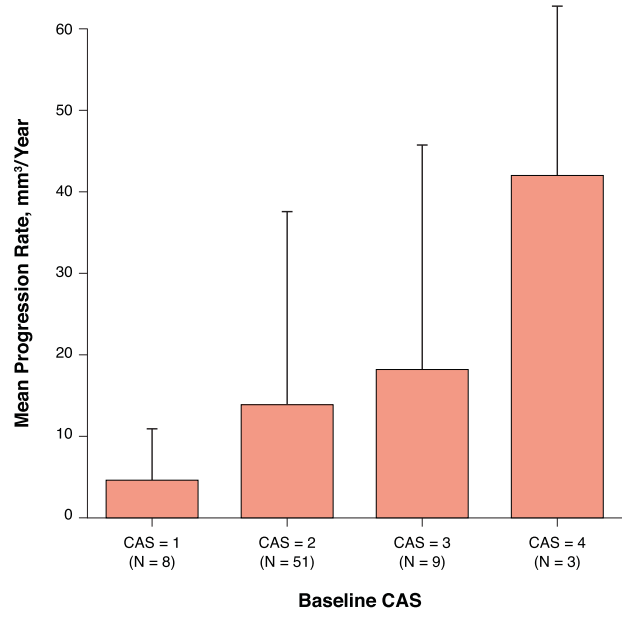

Figure 2. Mean Annualized Change in Wall Volume of Subjects Grouped According to Baseline CAS

The vertical bars represent 1 SD. Abbreviation as in Figure 1.

were coincident with DLS). All new DLS were found in those with CAS 3 or 4 at baseline (Fig. 1). There was a significant increasing trend for new DLS with increasing baseline CAS ($p < 0.001$) but not with new IPH ($p = 0.3$).

Plaque progression during follow-up. Two participants with evidence of new ulceration at follow-up were excluded from the plaque progression analysis (1 with baseline CAS = 3 and the other with CAS = 4). The mean progression rate was 14.6 ± 23.5 mm^3/year ($p < 0.001$ for comparison with 0) in the remaining 71 subjects. Figure 2 shows the mean progression rates within the subgroups defined according to baseline CAS. There was a significant increasing trend by linear regression ($p = 0.03$) between the mean progression rates of 4.7, 13.9, 18.1, and 42.0 mm^3/year and baseline CAS 1, 2, 3, and 4, respectively.

Comparison of CAS, carotid stenosis, and plaque burden measurements in predicting new DLS and IPH. Receiver-operating characteristic curve analysis was conducted with new DLS and IPH as outcomes and baseline CAS, stenosis, and plaque burden (wall volume, mean NWI, and maximum WT) as predictors (Table 4). CAS had the highest AUC (0.96 [95% confidence interval (CI): 0.92 to 1.0]) among predictors for new DLS (Fig. 3), whereas mean NWI and maximum WT had the highest AUC for predicting new IPH (0.78, $p > 0.06$ for both) (Fig. 4). The AUCs for carotid percent stenosis were 0.65 ($p = 0.2$) and 0.74 ($p = 0.1$) for new DLS and IPH, respectively. None of the variables considered were significantly associated with new IPH. When the combined outcome of new DLS or IPH was examined, CAS had the highest AUC (0.86 [95% CI: 0.71 to 1.0]), followed closely by mean NWI (0.84 [95% CI: 0.70 to 0.99]).

Comparison of CAS and severity of carotid stenosis in predicting plaque burden progression. The correlations between the plaque progression rate and baseline CAS, stenosis, and plaque burden are summarized in Table 5. CAS had the highest correlation ($r = 0.26$ [95% CI: 0.03 to 0.47]), whereas percent stenosis had the lowest ($r = -0.06$ [95% CI: −0.29 to 0.18]). The 3 plaque burden measures had similar levels of correlation (with progression of $r = 0.22$ to 0.23), but there were only trends toward significance ($p < 0.1$ for all 3 measures).

Table 4. Predicting New DLS or IPH Using a Single Baseline Predictor: CAS, Stenosis, or a Plaque Burden Measure (Subjects Without DLS or IPH at Baseline)

	Outcome					
	DLS		IPH		DLS or IPH	
	AUC (95% CI)	p Value*	AUC (95% CI)	p Value*	AUC (95% CI)	p Value*
CAS	0.96 (0.92–1.00)	<0.001	0.68 (0.42–0.94)	0.142	0.86 (0.71–1.00)	<0.001
Stenosis	0.65 (0.43–0.88)	0.183	0.74 (0.52–0.96)	0.110	0.69 (0.50–0.89)	0.063
Wall volume	0.58 (0.36–0.81)	0.465	0.74 (0.43–1.00)	0.104	0.59 (0.37–0.81)	0.383
Mean NWI	0.84 (0.67–1.00)	0.003	0.78 (0.60–0.95)	0.065	0.84 (0.70–0.99)	0.001
Maximum WT	0.75 (0.60–0.90)	0.030	0.78 (0.59–0.97)	0.062	0.76 (0.62–0.90)	0.013

*Test for AUC >0.5. p values were computed using an exact method and are therefore more reliable than the confidence intervals (CIs), which were computed using an approximation.
AUC = area under the receiver-operating characteristic curve; NWI = normalized wall index; WT = wall thickness; other abbreviations as in Table 3.

DISCUSSION

The initial formulation and testing of CAS was based on data from a cross-sectional study (17). The serial carotid MRI study reported herein demonstrates that CAS measures are predictive of future carotid luminal surface disruption, thus providing prospective confirmation of the earlier single time-point study findings. Furthermore, a significant association was noted between CAS and plaque progression in asymptomatic patients with 50% to 79% stenosis and who did not have carotid DLS or IPH at baseline. We caution the reader against over-interpretation of the data presented given the relatively low number of events. Nevertheless, the data are promising for a simplification

of carotid risk stratification using CAS and provide strong evidence for conducting future studies that use a larger study sample to validate these initial findings.

Findings from randomized clinical trials indicate that the benefit of CEA or stenting in this group of individuals is marginal. However, the further risk stratification offered by CAS has the potential to target subgroups that may benefit from intervention, although this possibility must be confirmed in a randomized clinical trial. CAS may also provide a means to identify individuals who would benefit from more intensive clinical follow-up. Although reliable multivariate analysis could not be conducted due to the limited sample size and event rate, CAS seemed to be more strongly associated with both plaque progression and new DLS than percent stenosis. This finding suggests that CAS may provide a better assessment of risk of stroke, beyond the current clinical angiographic solution, for asymptomatic patients with 50% to 79% stenosis.

Because maximum %LRNC is the major input variable to CAS, the finding that CAS is positively associated with the incidence of new DLS ($p < 0.001$) is consistent with the relationship between %LRNC volume and DLS previously reported by Underhill et al. (26). In the previous study, IPH was present in nearly 30% of the carotid arteries at baseline. In the present study, it was shown that the risk associated with LRNC, as represented by CAS, holds in the subgroup without IPH at baseline.

Although baseline CAS predicted incident DLS during follow-up, its relationship with new IPH was inconclusive. There were only 4 incidences of new IPH, and a positive association between CAS and new IPH was not found. However, all of the new episodes of IPH occurred in subjects with CAS 2 and 3 at baseline. For subjects with CAS 4, 78% of them had IPH already at baseline. Although a conclusion cannot be drawn from the small number of events seen here, this finding may suggest that IPH tends to occur at an earlier stage of plaque development and leads to growth into the higher levels of CAS, which is consistent with the concept of IPH as a primary driver of plaque growth, as shown previously (27,28).

The magnetic resonance plaque burden measure (mean NWI) seemed to predict new DLS or plaque progression well, although not better than CAS. During the original development of CAS, mean NWI was not considered, although maximum NWI was, as well as maximum WT and other plaque burden measures. In that cross-sectional analysis, maximum %LRNC area was more strongly associated with DLS and IPH than any plaque burden

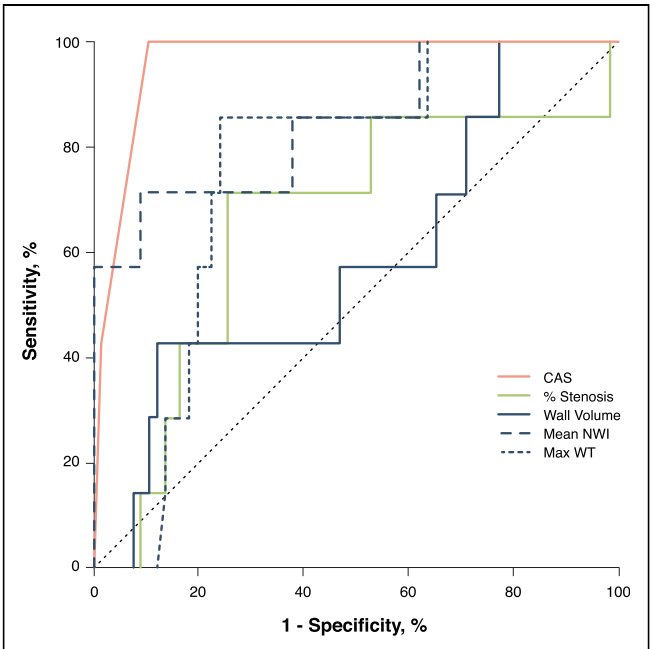

Figure 3. Receiver-Operating Characteristic Curves for Individual Predictors of New DLS

DLS = disrupted luminal surface; NWI = normalized wall index; WT = wall thickness; other abbreviation as in Figure 1.

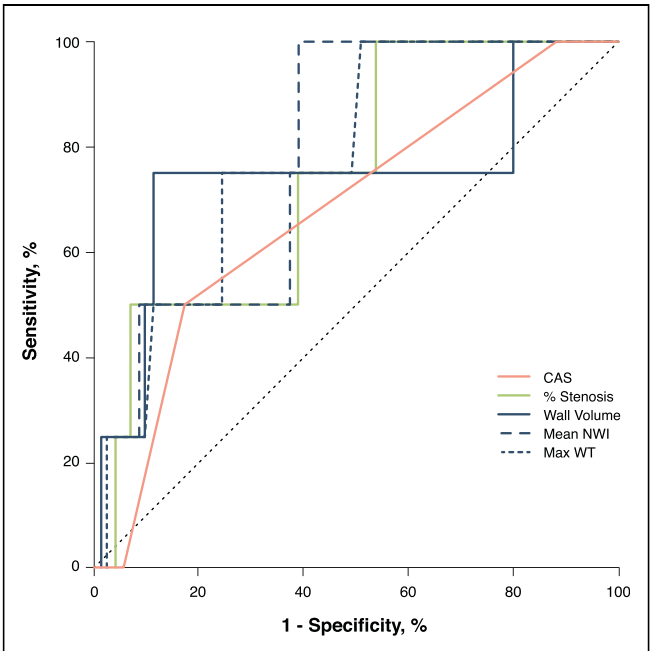

Figure 4. ROC Curves for Individual Predictors of New IPH

IPH = intraplaque hemorrhage; ROC = receiver-operating characteristic; other abbreviations as in Figures 1 and 3.

Table 5. Univariate Correlations Between Plaque Progression Over 3 Years and Baseline CAS, Stenosis, and Plaque Burden (71 Subjects Who Did Not Develop Ulceration Over Follow-Up)

	r (95% CI)	p Value
CAS	0.26 (0.03 to 0.47)	0.026
Stenosis	−0.06 (−0.29 to 0.18)	0.641
Wall volume	−0.22 (-0.02 to 0.43)	0.069
Mean NWI	−0.23 (-0.01 to 0.44)	0.057
Maximum WT	−0.22 (-0.01 to 0.43)	0.060

r = Pearson correlation coefficient; other abbreviations as in Table 4.

measures, and thus CAS was based primarily on LRNC rather than plaque burden. From a biological perspective, it is expected that CAS, which is based on the presence and size of the LRNC, will provide a more precise measure of risk for plaque disruption than mean NWI, which is based solely on plaque size. For large plaques that are predominantly fibrotic or calcified, the risk for disruption predicted according to mean NWI may vary from CAS. Future prospective studies may consider mean NWI as an additional predictor to confirm that this finding holds longitudinally.

Study limitations. The size of the study sample was not large, and subjects were recruited from only 2 related centers. Furthermore, the rate of new events and the prevalence of CAS 4 in subjects without DLS or IPH were small, which also prevented reliable multivariate analysis to statistically compare the different potential predictors. In addition, the association between the development of neurological symptoms and CAS could not be assessed due to the study design, which required subjects to have completed both a baseline and a 3-year follow-up MRI of their plaques. Clinical guidelines at the recruitment centers indicate CEA for patients with 50% to 79% stenosis according to ultrasound who become symptomatic, and thus no follow-up MRI was available in those cases. A larger, multicenter study is needed to have sufficient power to assess the ability of CAS for prediction of future ischemic events. Finally, 17% of patients were excluded in this study due to imaging issues. Three-dimensional MRI techniques such as 3D-MERGE and SNAP (29,30) have been recently developed that will reduce the percentage of excluded subjects in future studies. Advantages of these new techniques include: 1) larger field of view and isotropic 3-dimensional scans that will improve coregistration of serially acquired scans and reduce the number of cases excluded due to insufficient coverage; 2) shorter scan time, which may reduce exclusions due to motion artifact; 3) decreased artifact due to low flow; and 4) higher contrast between IPH, surrounding vessel wall, and lumen.

CONCLUSIONS

CAS, on the basis of 2 plaque parameters (maximum WT and %LRNC), was found to have a significant increasing relationship with incident DLS and plaque progression in this prospective, longitudinal study of subjects with asymptomatic, 50% to 79% carotid stenosis. The CAS concept provides a method to further stratify risk beyond luminal stenosis and may allow more effective targeting of patients for specific treatment to prevent future stroke.

Reprint requests and correspondence: Dr. Thomas S. Hatsukami, Vascular Imaging Laboratory, University of Washington, 850 Republican Street, Box 358050, Seattle, Washington 98109. *E-mail: tomhat@u.washington.edu.*

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